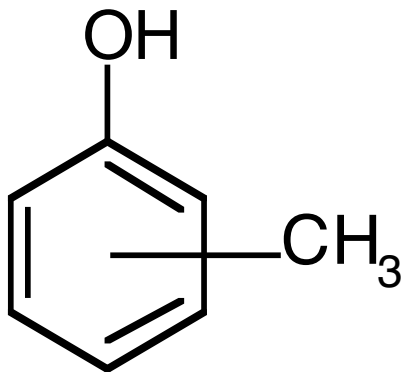
NTP
National Toxicology Program

Toxicology and Carcinogenesis Studies of Cresols in Male F344/N Rats and Female B6C3F1 Mice



Use and Human Exposure

- Used as intermediates in the production of antioxidants, fragrances, herbicides, insecticides, dyes and explosives. Used as disinfectants, preservatives, and solvents.

- Present in some plant oils. *p*-Cresol formed endogenously from tyrosine. Formed from combustion of coal and wood. Distilled from petroleum and coal tar. Produced from toluene.

- Present in vehicle emissions, cigarette smoke, some foods and beverages, wood creosote, and various other consumer products.

- Detected in air, sediment, soil, water; highest concentrations near point sources.

- Decay rapidly in the environment, but may persist in ground water at concentrations up to mg/L near landfills and hazardous waste sites.

Cresols: Study Rationale

- Nominated by the NIEHS for toxicity and carcinogenicity studies because:
  - High production chemicals.
  - Potential for occupational and consumer exposure.
  - Lack of chronic toxicity data.

Cresols: Genetic Toxicology

Cresol	*in vitro* mutagenicity		*in vivo* clastogenicity	
			Mouse MN test	
	Salmonella	*E. Coli*	Male	Female
ortho-	negative	negative	negative	negative
meta-	negative	negative		
para-	negative	negative		
m-/p-[a]	negative	negative	negative	negative

[a] Common cresol mixture composed of 60:40 *m*- and *p*-cresols

Cresols: 28-Day Studies in Male and Female F344/N Rats and B6C3F1 Mice (Reported in NTP TOX 9)

- **Exposure:** 0, 1000, 3000, 10,000, or 30,000 ppm; *o*-, *m*-, *p*-, or *m*-/*p*-cresol administered in feed.
- **Rats**
  - No mortality.
  - Clinical signs only in 30,000 ppm-exposed *p*- and *m*-/*p*-cresol groups.
  - Hyperplasia observed in nasal passages of males and females exposed to *p*- or *m*-/*p*-cresol (≥ 1000 ppm); and in esophagus (≥ 3000 ppm) and forestomach (≥ 10,000 ppm) of males and females exposed to *m*-/*p*-cresol.
- **Mice**
  - Some deaths, including all mice exposed to 30,000 ppm *p*-cresol.
  - Clinical signs for all cresols, mostly at 30,000 ppm.
  - Hyperplasia observed in nasal passages of males and females exposed to *p*- or *m*-/*p*-cresol (≥ 300 ppm). Hyperplasia of esophagus and forestomach observed in one male exposed to 30,000 ppm *m*-/*p*-cresol.

Cresols: 13-Week Studies (Nonneoplastic lesions)

o-Cresol (in feed)

Rats: 0, 1880, 3750, 7500, 15,000, or 30,000 ppm; Mice: 0, 1250, 2500, 5000, 10,000, or 20,000 ppm

Treatment Group	Lesion	Increased Incidence
Male and female rats	Bone marrow, Hypercellularity	30,000
Male and female mice	Forestomach epithelium, Hyperplasia	20,000

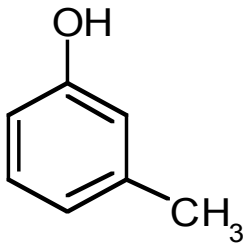
m-/*p*-Cresol (in feed)

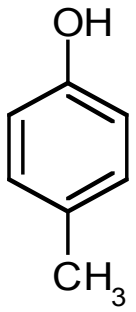
Rats: 0, 1880, 3750, 7500, 15,000, or 30,000 ppm; Mice: 0, 625, 1250, 2500, 5000, or 10,000 ppm

Treatment Group	Lesion	Increased Incidence (male; female)
Male and female rats	Bone marrow, Hypercellularity **Respiratory epithelium, Hyperplasia and glandular hyperplasia** Thyroid gland, Follicle, Increased colloid	30,000 3750; 7500 3750 15,000; 7500
Female rats	Uterus, Atrophy	30,000
Male mice	**Respiratory epithelium, Hyperplasia**	10,000

Cresols: 2-Year Studies

■ **Test chemical: 60:40 mixture of *m- and p*-Cresol (*m*-/*p*-cresol)**





CAS No. 1319-77-3
Chemical Formula: C_7H_8O
Molecular Weight: 108.14

- A common cresol mixture. Representative of the isomeric ratio of *m* and *p* distilled from coke-oven tars.
- More histopathological effects than for *o*-cresol in the 13-week studies.

Cresols: 2-Year Studies, con't.

- **Studied in male F344/N rats and female B6C3F1 mice.**
  - Majority of NTP rodent carcinogens identified in either or both groups.
  - Adequate paradigm for cresols because they are members of a well-studied class of chemicals. (Phenol and toluene were negative for carcinogenicity in traditional two species-both sexes protocol).

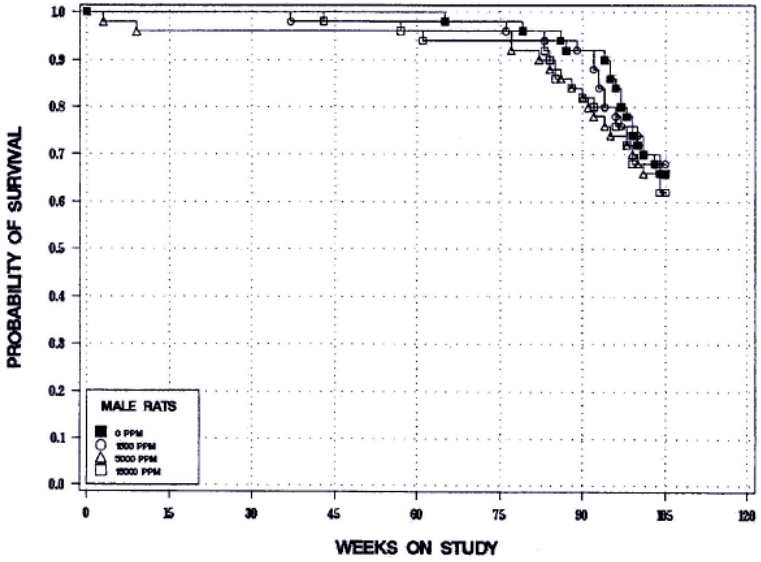
- **Oral route of exposure**
  - Administered in feed.

- **Concentrations in feed (determined by results of 13-week studies):**
  - Rats: 0, 1500, 10,000, or 15,000 ppm.
  - Mice: 0, 1000, 3000, or 10,000 ppm.

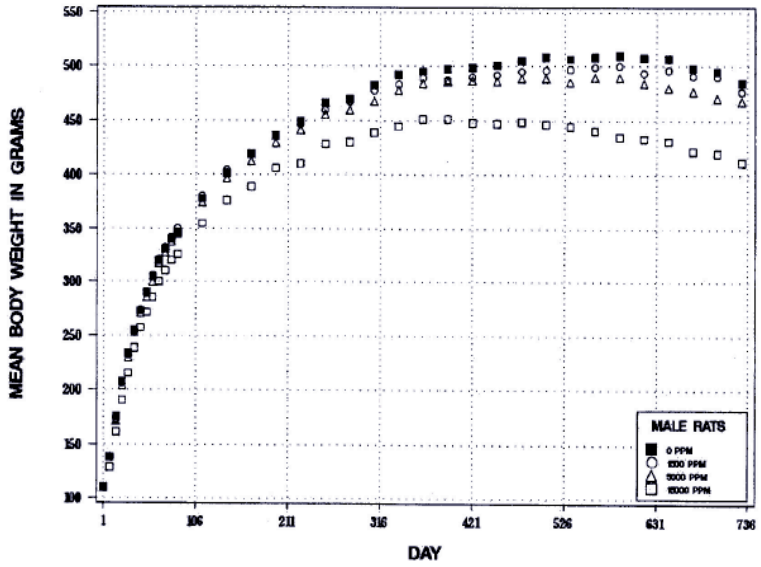
Results of the 2-Year Study in Male F344/N Rats

(0, 1500, 10,000, or 15,000 ppm)

Survival curves



Growth curves



- No effect on survival.
- Decreased body weight gain at 15,000 ppm.

Neoplastic and Nonneoplastic Lesions of the Kidney in Male F344/N Rats

Lesion	Exposure concentration (ppm) 0	1500	5000	15,000
Renal tubule, Adenoma				
Standard evaluation	0[a]	0	0	3[b]
Standard + Extended evaluation	0	0	0	4[c]
Renal tubule, Hyperplasia (combined)	5	0	1	1
Transitional epithelium, Hyperplasia	0	0	2 (2.0 [d])	8**(1.9)
Nephropathy	47 (1.4)	48 (1.4)	46 (1.7)	49 (2.1)

[a] Animals with lesion; n = 50
[b] p = 0.109; Exceeds the range (0-2%) of historical controls
[c] p = 0.054
[d] Average severity grade of lesion

** p ≤ 0.01

Selected Nonneoplastic Lesions in Male F344/N Rats

Site	Lesion	Exposure conc. (ppm)			
		0	1500	5000	15,000
Liver	Eosinophilic focus	14[a]	14	13	23*
Nose	Inflammation	17	19	19	28*
Nose, Goblet cell	Hyperplasia	23	40**	42**	47**
Nose, Respiratory epithelium	Hyperplasia	3	17**	31**	47**
	Metaplasia	0	1	8**	40**

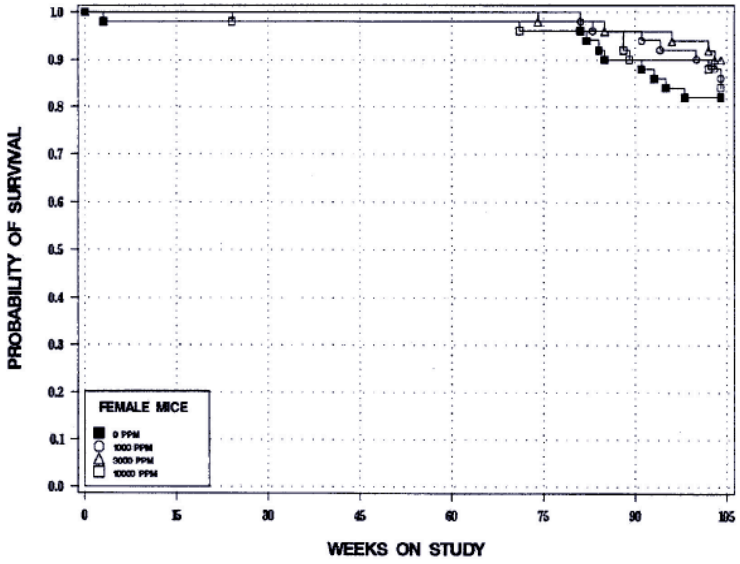
[a] Animals with lesion; n = 50

* $p \leq 0.05$
** $p \leq 0.01$

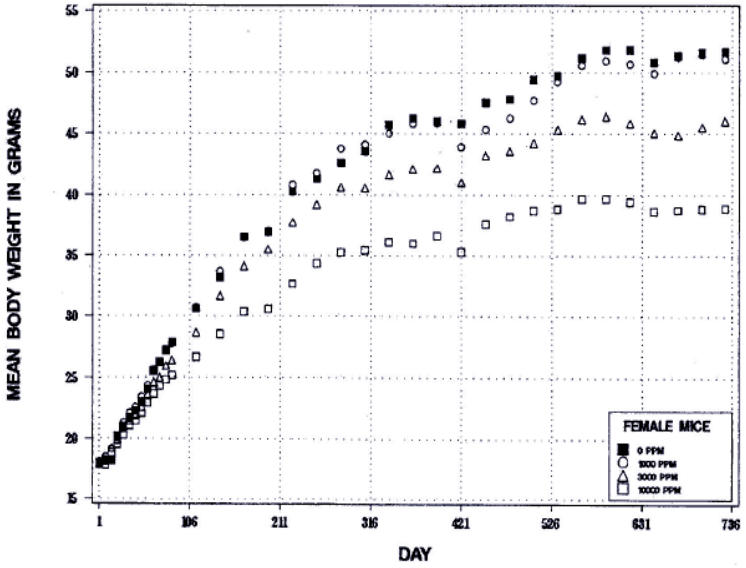
Results of the 2-Year Study in Female B6C3F1 Mice

(0, 1000, 3000, or 10,000 ppm)

Survival curves



Growth curves



- **No effect on survival.**
- **Severe decreased body weight gain at 10,000 ppm.**
  - **Mean final body weight was 25% lower than control.**
  - **Feed consumption was 13% lower than control.**

Neoplastic and Nonneoplastic Lesions of the Forestomach in Female B6C3F1 Mice

Lesion	Exposure concentration (ppm)			
	0	1000	3000	10,000
Squamous cell papilloma	0[a]	1	1	10***
Epithelium, Hyperplasia	0	0	0	2

[a] Animals with lesion; n = 49-50

*** $p < 0.001$

Selected Nonneoplastic Lesions in Female B6C3F1 Mice

Site	Lesion	Exposure conc. (ppm)			
		0	1000	3000	10,000
Thyroid	Follicular degeneration	7[a]	24**	24**	21**
Liver	Eosinophilic focus	1	0	2	12**
Nose, Respiratory epithelium	Hyperplasia	0	0	28**	45**
Lung, Bronchiole	Hyperplasia	0	42**	44**	47**

[a] Animals with lesion; n = 48-50

** $p \leq 0.01$

Conclusions of the 2-Year Study in Male F344/N Rats

- There was *equivocal evidence of carcinogenic activity* of 60:40 *m*-/*p*-cresol in male F344/N rats based on the marginally increased incidence of renal tubule adenoma.
- Nonneoplastic lesions (inflammation, hyperplasia, and metaplasia) related to cresol exposure were observed in the nasal passages.
- Nonneoplastic lesions related to cresol exposure were observed in the kidney and the liver.

Conclusions of the 2-Year Study in Female B6C3F1 Mice

- There was *some evidence of carcinogenic activity* of 60:40 *m*-/*p*-cresol in female B6C3F1 mice based on the increased incidence of forestomach squamous cell papilloma.

- Nonneoplastic lesions related to cresol exposure were observed in the respiratory tract (hyperplasia in the nasal passages and the lung).

- Nonneoplastic lesions related to cresol exposure were observed in the thyroid and the liver.